201-15141

HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

Propanoic acid, 3,3'-thiobis-, dimethyl ester

CAS No. 4131-74-2

Submitted to the US EPA

BY

Crompton Corporation.

Table of Contents

Test Plan for Dimethyl 3,3'-thiobispropionate

1. General Information

1.1 CAS Number: 4131-74-2

1.2 Molecular Weight: 206.26

1.3 Structure and formula: $C_8H_{14}O_4S$

$S(CH_2CH_2CO_2CH_3)_2$

1.4 Introduction

Propanoic acid, 3,3'-thiobis-, dimethyl ester is used as an antioxidant in PVC systems.

2. Justification for Use of Read Across Data for Human Health Toxicity Endpoints

Studies have been reported in the literature concerning the metabolism of thiodipropionic acid (TDPA) and its esters (see robust summary section 5). These studies show that esters of TDPA are almost completely absorbed and hydrolysed to TDPA, which itself is largely eliminated in the urine, either as the free acid or as an acid labile conjugate. Absorption of the various esters of TDPA is not significantly affected by the water solubility as demonstrated by the high degree of absorption of one analog, didodecyl 3,3'-thiodipropionate (insoluble in water), following oral administration in the rat. Radiolabeled studies show esters of TDPA will undergo hydrolytic cleavage. This process can occur to a significant extent within the gastrointestinal tract. It is therefore likely that any toxicity, or lack of toxicity, will be as a consequence of exposure to hydrolytic degradants, particularly the parent acid. It can be predicted that TDPA will be the most significant degradant following oral ingestion of dimethyl 3,3'-thiodipropionate, therefore the toxicity of this product has been evaluated indirectly from toxicity studies with didodecyl 3,3'-thiodipropionate.

3. Review of Existing Data and Development of Test Plan

Crompton Corporation has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for Propanoic acid, 3,3'-thiobis-, dimethyl ester and structural analogs.

The availability of the data on the specific SIDS endpoints is summarized in Table 1. Table 1 also shows data gaps that will be filled by additional testing.

Table 1: Available adequate data and proposed testing on Propanoic acid, 3,3'-thiobis-, dimethyl ester

CAS No. 4131-74-2	Information Available?	GLP	OECD Study?	Other Study?	Estimation Method?	Acceptable?	SIDS Testing required?
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physicochemical							
Melting Point	Y	N			Y	Y	N
Boiling Point	Y	N			Y	Y	N
Vapour Pressure	Y	N			Y	N	Y
Water Solubility	Y	N			Y	N	Y
Partition Coefficient (Kow)	Y	N			Y	Y	N
Environmental Fate							
Biodegradation	Y				Y	N	Y
Hydrolysis	Y				Y	Y	N
Photodegradation	Y				Y	Y	N
Transport and Distribution between Environmental Compartments	Y				Y	Y	N
Ecotoxicology							
Acute Fish	Y				Y	Y	N
Acute Daphnia	Y				Y	Y	N
Acute Algae	Y				Y	Y	N
Toxicology							
Acute Oral	Y*					Y	N
Repeat Dose toxicity	Y*					Y	N
Genetic toxicity – Gene mutation	N					N	Y
Genetic toxicity – Chromosome aberration	N					N	Y
Reproductive toxicity	Y*					Y	N
Developmental toxicity/teratogenicity	Y*					Y	N

* Data available on analogs

A. Evaluation of Existing Physicochemical Data and Proposed Testing

1. Melting Point

The substance is a liquid at room temperature. The melting point is estimated to be –38.3°C using MPBPWIN v1.40.

2. Boiling Point

The boiling point (literature) ranged from 130°C at 2mm Hg to 148°C at 18mm Hg.

3. Vapour Pressure

A vapour pressure study will be conducted following OECD guidelines.

4. Water Solubility

A water solubility study will be conducted following OECD guidelines.

5. Partition Coefficient

The partition coefficient is estimated as log Kow = 0.98 using KOWWIN v1.66.

Summary of Physicochemical Properties Testing: Existing data for melting point, boiling point, and partition coefficient are considered to fill these endpoints adequately. A vapour pressure and water solubility test will be conducted.

B. Evaluation of Existing Environmental Fate Data and Proposed Testing

1. Biodegradation

The biodegradability of the chemical has been estimated using Biowin v4.00 and the results indicate the chemical to be readily biodegradable. A Biodegradation study will be conducted following OECD guidelines.

2. Hydrolysis

The half life is estimated to be 1.02 years at pH7 using HYDROWIN v1.67.

3. Photodegradation

The potential for photodegradation has been estimated using the AOPWIN v1.90, and indicates atmospheric oxidation via OH radicals reaction with a half-life of 6.2 hours.

4. Transport and Distribution between Environmental Compartments

An Epiwin Level III Fugacity Model calculation has been conducted for the chemical and indicates distribution mainly to water and soil for emissions of 1000 kg/hr simultaneously to air water and soil compartments. The fugacity model estimates will be recalculated once measured data on the vapour pressure and water solubility are available.

Summary of Environmental Fate Testing: The endpoints for biodegradation, hydrolysis, photodegradation and transport and distribution between environmental compartments are filled adequately. No additional testing is recommended.

C. Evaluation of Existing Ecotoxicity Data and Proposed Testing

1. Acute Toxicity to Fish

   The LC50 (96 h) is estimated to be 109.7 mg/L, calculated using ECOSAR v0.99g.

2. Acute Toxicity to Algae

   The EC50 (96 h) is estimated to be 8.41 mg/L, calculated using ECOSAR v0.99g.

3. Acute Toxicity to Daphnia

   The EC50 (48 h) is estimated to be 1388.7 mg/L, calculated using ECOSAR v0.99g.

Summary of Ecotoxicity Testing: No further ecotoxicity testing is recommended due to the extremely low water solubility and high estimated log K_{ow} value. The ecotoxicity endpoints are considered to be adequate. However based on the measured water solubility data and the recalculated fugacity model data, the ecotoxicity testing will be re-evaluated.

D. Evaluation of Existing Human Health Effects Data and Proposed Testing

1. Acute Oral Toxicity

   The LD_{50} (rat) has been reported as between >2500 and >5000 mg/kg b.w. and LD50 (mouse) as >2000 in studies conducted using the analog didodecyl 3,3'-thiodipropionate. In studies using the parent thiodipropionic acid, LD_{50} (mouse) of 2000 mg/kg b.w. and LD50 (rat) of 3000 mg/kg b.w. were reported.

2. Repeat Dose Toxicity

   In a repeat dose toxicity study (oral, 13 weeks, rat) using the analog didodecyl 3,3'-thiodipropionate a NOAEL of 350 mg/kg b.w./day was reported.

3. Genotoxicity

   Adequate genetic toxicity data are available for the analog in the thiodipropionates category and the results from both the tests are negative.

4. Reproductive and Developmental Toxicity

In a study using the analog didodecyl 3,3'-thiodipropionate (oral, 13 week, rat) no adverse effects were seen in the reproductive organs of the test animals up to and including the high dose of 1000 mg/kg b.w./day. This is suggestive of no adverse effects on reproduction.

Developmental toxicity studies have been conducted using the analog didodecyl 3,3'-thiodipropionate (oral, essentially following OECD 414, rat, mouse, rabbit, hamster). In all these studies, no adverse effects were seen in the parents or the offspring at the highest dose used.

Summary of Human Health Effects Testing: Existing data for the analog from and parent thiopropionic acid are considered adequate for Health Effects endpoints and no further testing is recommended.

3. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance [2] and the systematic approach described by Klimisch et al [3]. These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation [4]. The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g. listed in abstracts or secondary literature.

4. References

[1] US EPA, EPI Suite Software, 2000

[2] USEPA (1998). Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

[3] Klimisch, H.-J., et al (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul. Toxicol. Pharmacol. 25:1-5

[4] USEPA (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.